What is claimed is:

1. A method for identifying a drug candidate as an HIV protease inhibitor potentially resistive against loss of inhibitory activity due to development of resistant strains of HIV, the method comprising the following steps:

Step A: determining whether the drug candidate has a binding activity with respect to HIV protease of less than 1 μM;

Step B: determining whether the drug candidate has an inhibitory activity with respect to HIV protease of less than 1 μM;

Step C: determining whether the drug candidate has a binding activity with respect to FIV protease of less than 1 μM;

Step D: determining whether the drug candidate has an inhibitory activity with respect to FIV protease of less than 1 μM; and then

Step E: if, in said Steps A, B, C, and C, the drug candidate is determined to have binding and inhibitory activities with respect to both HIV protease and FIV protease of less than 1 μM, then selecting the drug candidate as the HIV protease inhibitor potentially resistive against loss of inhibitory activity due to development of resistant strains of HIV.

2. A method for synthesizing a drug candidate for inhibiting HIV protease, the drug candidate including an N-terminus, a C-terminus, and an α-keto amide core structure linking the N-terminus and the C-terminus, the N-terminus incuding an aromatic amino acid residue selected from the group consisting of phenylalanine, tyrosine, and O-substituted tyrpsine, the aromatic amino acid including a carbonyl group for linking to and incorporation into the α-keto amide core structure, the C-terminus including a heterocyclic ring having a ring nitrogen and one or more substitutions, the ring nitrogen of the C-terminus for linking to and incorporation into the α-keto amide core structure, the method comprising the following steps:

Step A: providing an N-terminus precursor identical to the N-terminus except that the carbonyl group is replaced by an α-hydroxyl acid group;

Step B: providing a C-terminus precursor identical to the C-terminus except that the ring nitrogen forms a secondary amine;

Step C: coupling the N-terminus precursor of said Step A to the C-terminus precursor of said Step B to form a drug candidate precursor indentical to the drug candidate except that the α-keto amide core structure of the drug candidate is replaced by an α-hydroxyl amide core stucture linking and incorporating the carbonyl group of the N-terminus and the ring nitrogen of the C-terminus; and then

Step D: oxidizing the α-hydroxyl amide core stucture of the drug candidate precursor of said

Step C for forming the α-keto amide core structure and the drug candidate.

3. A method for synthesizing a library of nxm drug candidates for inhibiting HIV protease, each of the nxm drug candidates including an N-terminus selected from **n** N-termini where **n** is two or greater, a C-terminus selected from **m** C-termini where **m** is two or greater, and an α-keto amide core structure linking the N-terminus and the C-terminus, each of the **n** N-termini incuding an aromatic amino acid residue selected from the group consisting of phenylalanine, tyrosine, and O-substituted tyrosine, the aromatic amino acid including a carbonyl group for linking to and incorporating into the α-keto amide core structure, each of the **m** C-termini including a heterocyclic ring having a ring nitrogen and one or more substitutions, the ring nitrogen of the C-terminus for linking to and incorporating into the α-keto amide core structure, the method comprising the following steps:

Step A: providing **n** N-terminus precursors identical in structure to the **n** N-termini except that the carbonyl group of the N-termini is replaced by an α-hydroxyl acid group within the N-terminus precursors;

Step B: providing **m** C-terminus precursors identical in structure to the **m** C-termini except that the ring nitrogen of the C-termini forms a secondary amine within the C-terminus precursors;

Step C: providing nxm reaction vessels;

Step D: loading each of the **n** N-terminus precursors into **m** of the reaction vessels of said Step C;

Step E: loading each of the **m** C-terminus

precursors into n of reaction vessels of said Step D for forming nxm admixtures of N-terminus precursor and C-terminus precursors; then

Step F: within each of the nxm admixtures of said Step E, coupling the N-terminus precursor to the C-terminus precursor to form nxm drug candidate precursors identical to the nxm drug candidates except that the α-keto amide core structure of the nxm drug candidates is replaced by an α-hydroxyl amide core stucture linking and incorporating the carbonyl group of the N-terminus and the ring nitrogen of the C-terminus; and then

Step G: within each of the nxm reaction vessels, oxidizing the α-hydroxyl amide core stucture of each of the nxm drug candidate precursors of said Step F for forming the α-keto amide core structure and the library of nxm drug candidates.

4. A method for synthesizing a library of nxm drug candidates for inhibiting HIV protease, each of the nxm drug candidates including an N-terminus selected from n N-termini where n is two or greater, a C-terminus selected from m C-termini where m is two or greater, and a hydroxyethylamine core structure linking the N-terminus and the C-terminus, each of the n N-termini incuding an aromatic amino acid residue selected from the group consisting of phenylalanine, tyrosine, and O-substituted tyrosine, the aromatic amino acid including a hydroxyethyl group *in lieu* of a carbonyl group for linking to and incorporating into the hydroxyethylamine core

structure, each of the **m** C-termini including a heterocyclic ring having a ring nitrogen and one or more substitutions, the ring nitrogen of the C-terminus for linking to and incorporating into the hydroxyethylamine core structure, the method comprising the following steps:

Step A: providing **n** N-terminus precursors identical in structure to the **n** N-termini except that the hydroxyethyl group of the N-termini is replaced by an epoxide group within the N-terminus precursors;

Step B: providing **m** C-terminus precursors identical in structure to the **m** C-termini except that the ring nitrogen of the C-termini forms a secondary amine within the C-terminus precursors;

Step C: providing nxm reaction vessels;

Step D: loading each of the **n** N-terminus precursors into **m** of the reaction vessels of said Step C;

Step E: loading each of the **m** C-terminus precursors into **n** of reaction vessels of said Step D for forming nxm admixtures of N-terminus precursor and C-terminus precursors; then

Step F: within each of the nxm admixtures of said Step E, coupling the N-terminus precursor to the C-terminus precursor for forming the library of nxm drug candidates.

5. A library of nxm drug candidates for inhibiting HIV protease, each of the nxm drug candidates including an N-terminus selected from **n** N-termini

where **n** is two or greater, a C-terminus selected from **m** C-termini where **m** is two or greater, and an α-keto amide core structure linking the N-terminus and the C-terminus, each of the **n** N-termini incuding an aromatic amino acid residue selected from the group consisting of phenylalanine, tyrosine, and O-substituted tyrosine, the aromatic amino acid including a carbonyl group for linking to and incorporating into the α-keto amide core structure, each of the **m** C-termini including a heterocyclic ring having a ring nitrogen and one or more substitutions, the ring nitrogen of the C-terminus for linking to and incorporating into the α-keto amide core structure.

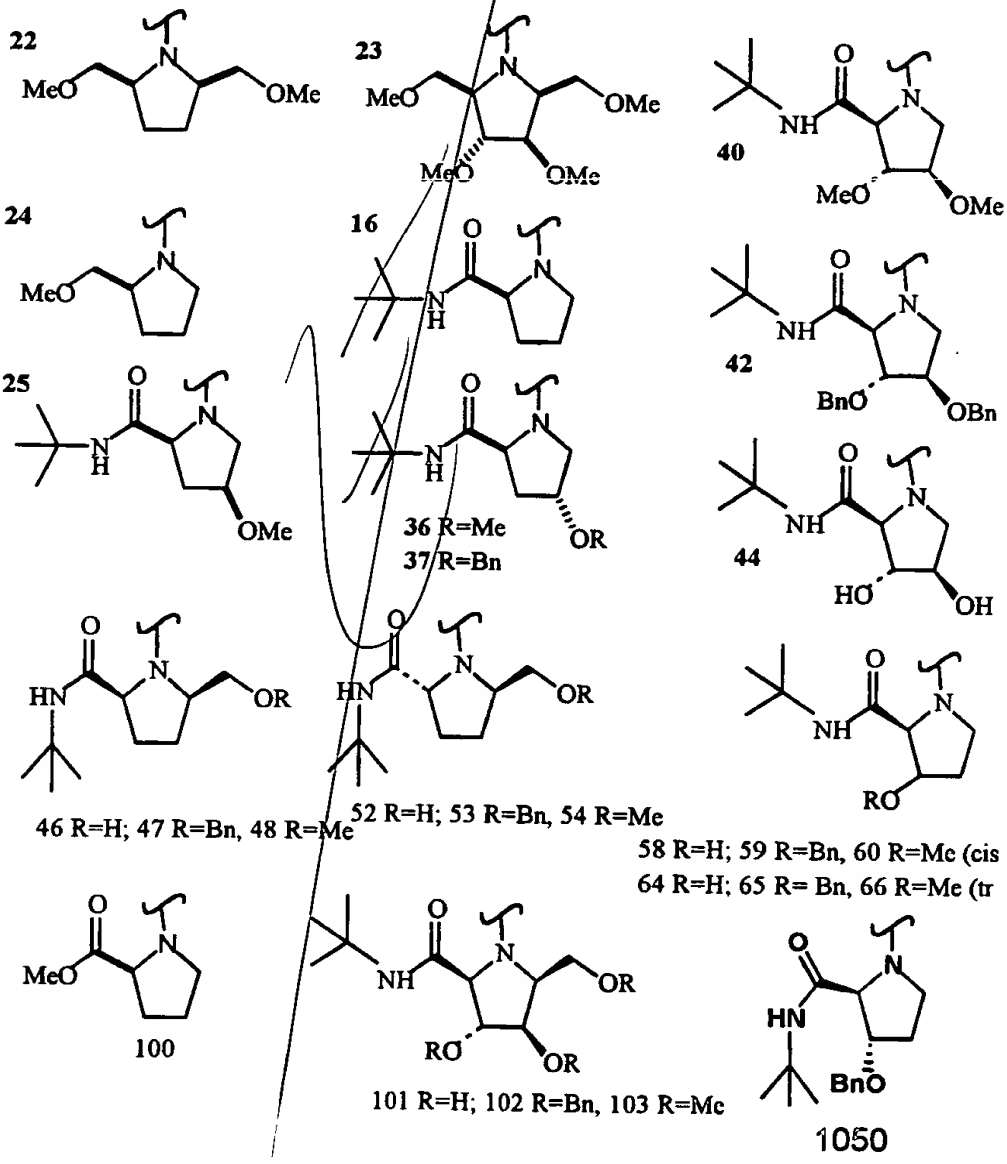
6. A library of nxm drug candidates for inhibiting HIV protease, each of the nxm drug candidates including an N-terminus selected from **n** N-termini where **n** is two or greater, a C-terminus selected from **m** C-termini where **m** is two or greater, and a hydroxyethylamine core structure linking the N-terminus and the C-terminus, each of the **n** N-termini incuding an aromatic amino acid residue selected from the group consisting of phenylalanine, tyrosine, and O-substituted tyrosine, the aromatic amino acid including a hydroxyethyl group *in lieu* of a carbonyl group for linking to and incorporating into the hydroxyethylamine core structure, each of the **m** C-termini including a heterocyclic ring having a ring nitrogen and one or more substitutions, the ring nitrogen of the C-terminus for linking to and incorporating into the hydroxyethylamine core structure.

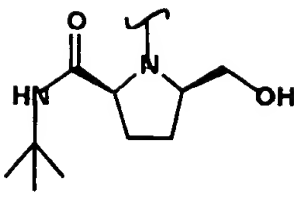
7. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

said core structure being an α-keto amide, and

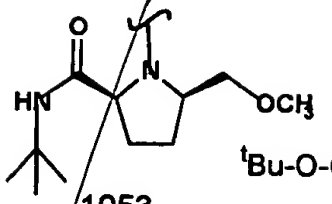
the heterocyclic ring of said N-terminus being a pyrrolidine having at least one substituant other than carboxylic acid and carboxymethyl ester.

8. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 7 wherein said pyrrolidine is selected from the group represented by the following structures:





1052



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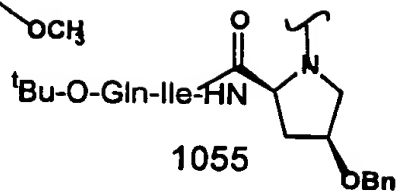

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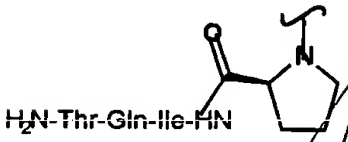

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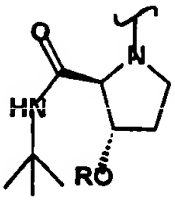
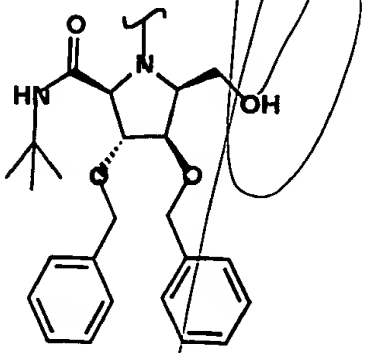
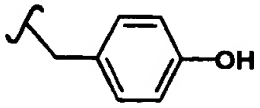
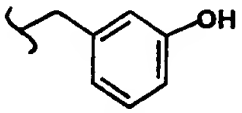
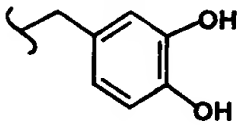




where:

1054 R = 

1059 R = 

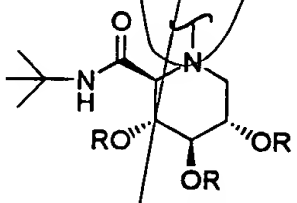
1060 R = 

9. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

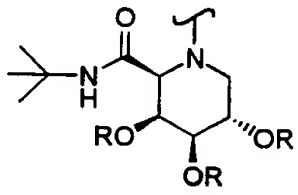
said core structure being an α-keto amide, and

the heterocyclic ring of said N-terminus being a piperadine or an azasugar.

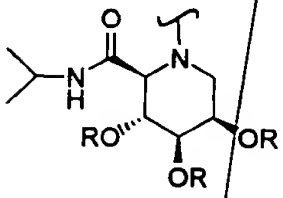
10. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 9 wherein said piperadine or azasugar is selected from the group represented by the following structures:



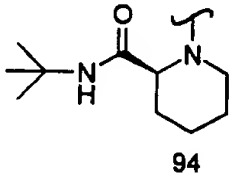
R = 85 H, 86 Me, 87 Bn



R = 88 H, 89 Me, 90 Bn



R = 91 H, 92 Me, 93 Bn



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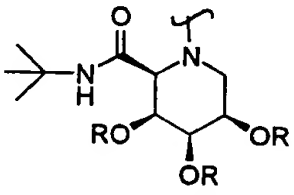


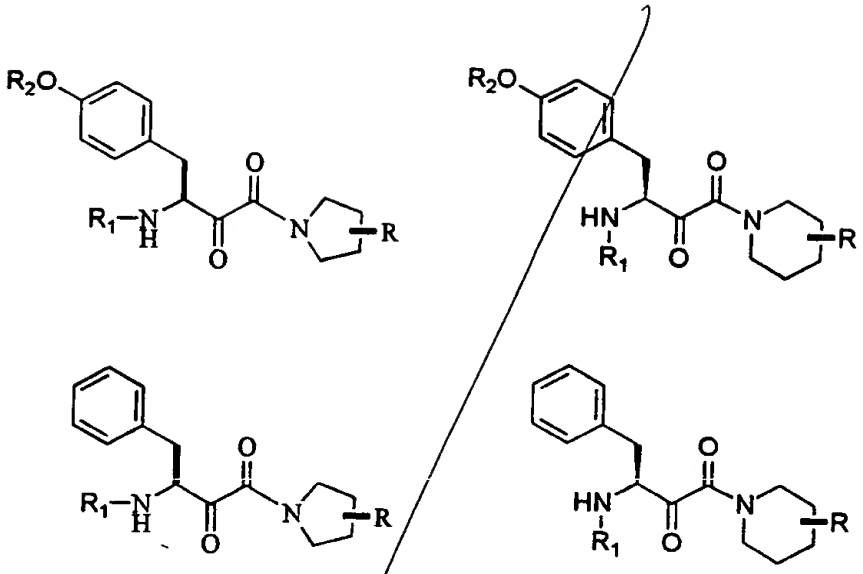
R = 95 H, 96 Me, 97 Bn

11. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

said core structure being an α-keto amide, and

the aromatic amino acid of said C-terminus being selected from a group consisting of tyrosine having a protected amino, tyrosine having a protected amino and a substituted hydroxyl, and phenylalanine having a protected amino protected by carbobenzyloxy.

12. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 11 selected from the group represented by the following structures:



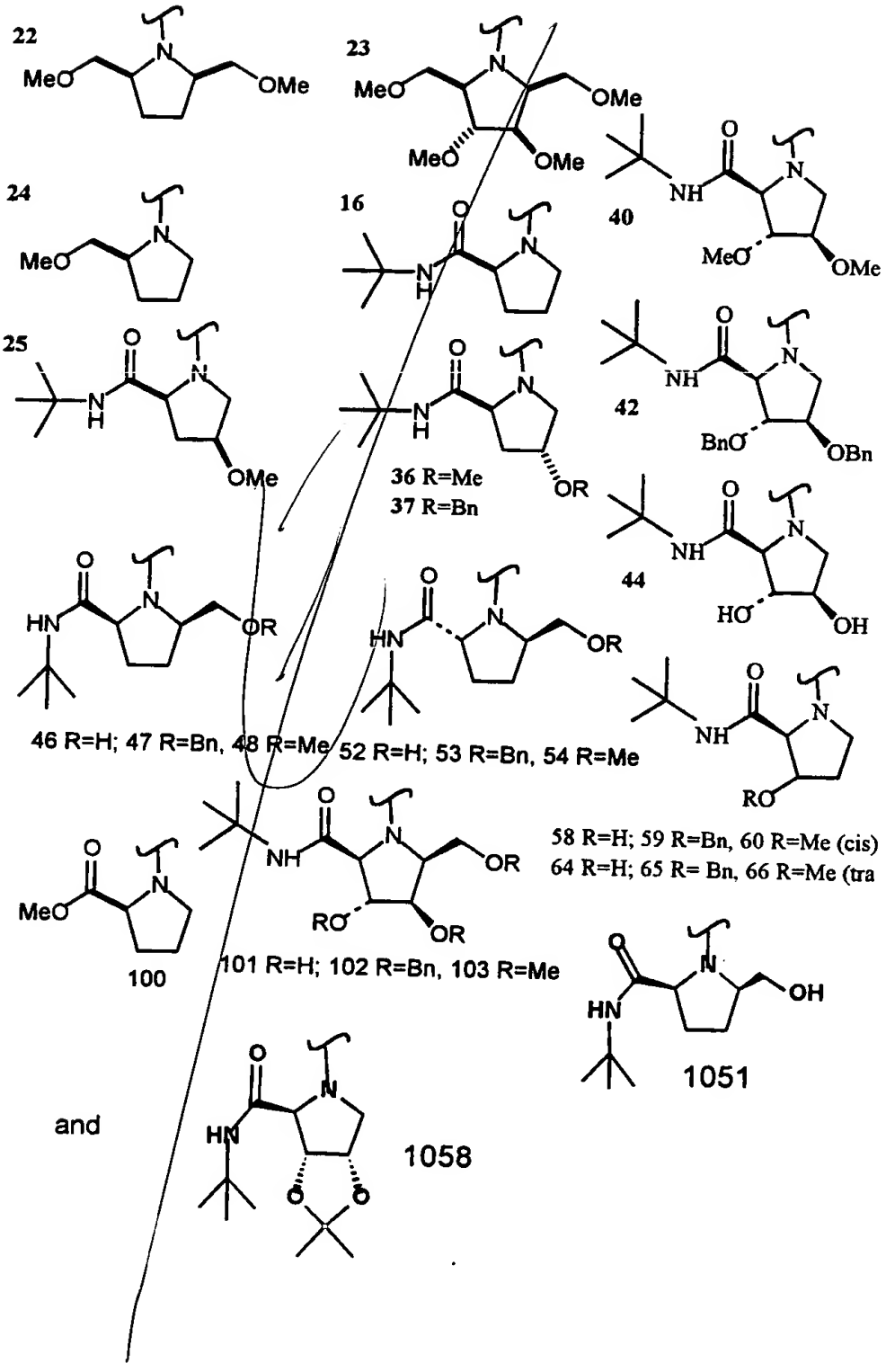
wherein R is selected from the group consisting of hydrogen, hydroxy, benzyloxy, alkyl$_{(C1-C4)}$-oxy, *o*-methoxy-benzyloxy, *m*-methoxy-benzyloxy, *p*-methoxy-benzyloxy, *o*-methoxy-nitrobenzyloxy, *m*-methoxy-nitrobenzyloxy, *p*-methoxy-nitrobenzyloxy, acetonide, benzylidene, 3-oxymethyl-catechol, 4-oxymethyl-catechol; R_1 is selected from the group consisting of carbobenzyloxy (CBZ), *tert*-butoxycarbonyl (*t*-BOC), acyl; R_2 is selected from the group consisting of hydrogen, benzyl, alkyl$_{(C1-C4)}$, *o*-methoxy-benzyl, *m*-methoxy-benzyl, *p*-methoxy-benzyl, *o*-methoxy-nitrobenzyl, *m*-methoxy-nitrobenzyl, *p*-methoxy-nitrobenzyl, 3-methylene-catechol, 4-methylene-catechol.

13. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

said core structure being hydroxyethylamine, and

the heterocyclic ring of said N-terminus being a pyrrolidine having at least one substituant other than carboxylic acid and carboxymethyl ester.

14. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 13 wherein said pyrrolidine is selected from the group represented by the following structures:

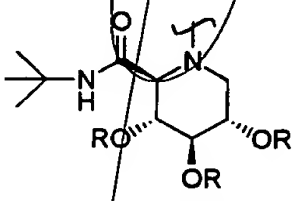

22
23
24
16
40
25
42
36 R=Me
37 R=Bn
44
46 R=H; 47 R=Bn, 48 R=Me
52 R=H; 53 R=Bn, 54 R=Me
58 R=H; 59 R=Bn, 60 R=Me (cis)
64 R=H; 65 R= Bn, 66 R=Me (tra
100
101 R=H; 102 R=Bn, 103 R=Me
1051
and
1058

15. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

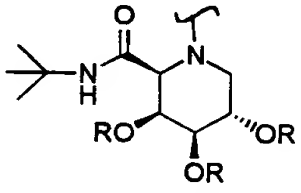
said core structure being hydroxyethylamine, and

the heterocyclic ring of said N-terminus being a piperadine or an azasugar.

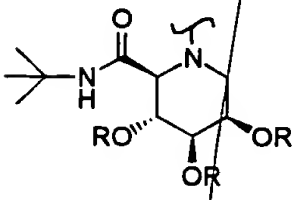
16. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 15 wherein said piperadine or azasugar is selected from the group represented by the following structures:



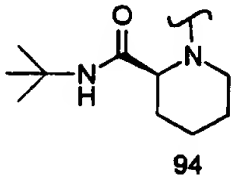
R = 85 H, 86 Me, 87 Bn



R = 88 H, 89 Me, 90 Bn



R = 91 H, 92 Me, 93 Bn



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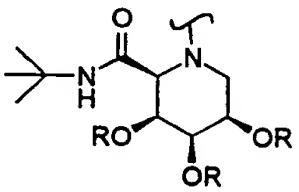


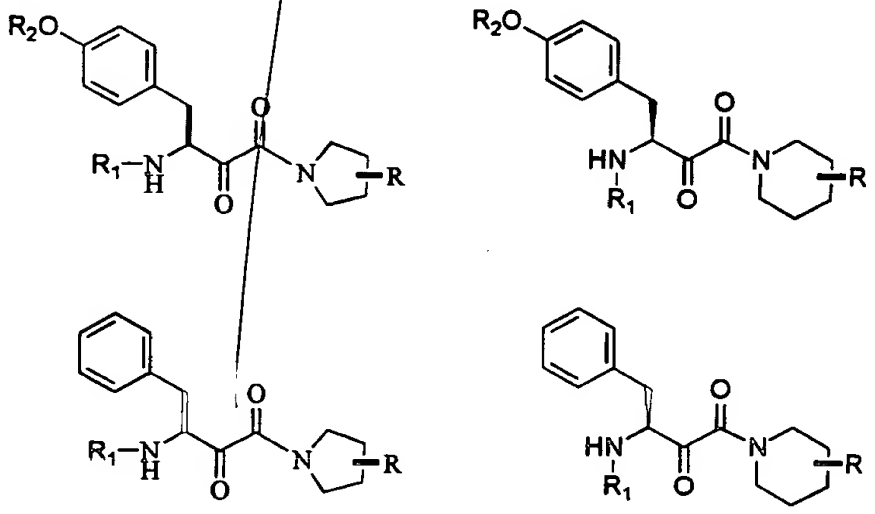
R = 95 H, 96 Me, 97 Bn

17. An improved mechanism based inhibitor of HIV or FIV aspartyl protease of a type having an N-terminus, a C-terminus, and a core structure for linking the N-terminus to the C-terminus, the N-terminus incuding an aromatic amino acid residue linked to said core structure, the C-terminus including a heterocyclic ring including a ring nitrogen linked to said core structure, the core structure being isosteric with a scissile amide bond of a HIV or FIV aspartyl protease substrate, wherein the improvement comprises:

said core structure being hydroxyethylamine, and

the aromatic amino acid of said C-terminus being selected from a group consisting of tyrosine having a protected amino, tyrosine having a protected amino and a substituted hydroxyl, and phenylalanine having a protected amino protected by carbobenzyloxy.

18. An improved mechanism based inhibitor of HIV or FIV aspartyl protease as described in claim 17 selected from the group represented by the following structures:



wherein R is selected from the group consisting of hydrogen, hydroxy, benzyloxy, alkyl$_{(C1-C4)}$-oxy, *o*-methoxy-benzyloxy, *m*-methoxy-benzyloxy, *p*-methoxy-benzyloxy, *o*-methoxy-nitrobenzyloxy, *m*-methoxy-nitrobenzyloxy, *p*-methoxy-nitrobenzyloxy, acetonide, benzylidene, 3-oxymethyl-catechol, 4-oxymethyl-catechol; R_1 is selected from the group consisting of carbobenzyloxy (CBZ), *tert*-butoxycarbonyl (*t*-BOC), acyl; R_2 is selected from the group consisting of hydrogen, benzyl, alkyl$_{(C1-C4)}$, *o*-methoxy-benzyl, *m*-methoxy-benzyl, *p*-methoxy-benzyl, *o*-methoxy-nitrobenzyl, *m*-methoxy-nitrobenzyl, *p*-methoxy-nitrobenzyl, 3-methylene-catechol, 4-methylene-catechol.